REMARKS

Claims 15, 19-23 and 37 were pending prior to this response. By the present communication, claims 15, 22 and 37 have been amended; no claims have been canceled; and no claims have been added. The amendments do not raise any issues of new matter being supported by the specification and claims as filed. Thus, upon entry of the present amendment, claims 15, 19-23 and 37 will be pending in this application.

The Office has objected to the title as allegedly not being indicative of the invention to which the claims are directed. Without acquiescing to the rationale of the Office, Applicants have amended the title to fully comply with the Examiner's requirements; such amendments being presented above. Accordingly, Applicants respectfully request all objections to the title be withdrawn.

Rejections under 35 U.S.C. §112, Second Paragraph

Applicants respectfully traverse the rejection of claims 15, 19-23, and 37 under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Specifically, the Office alleges that the claimed antibody "inhibits DNA synthesis" without any guidance as to under what conditions such synthesis would be inhibited. Applicants respectfully disagree for the reasons presented below.

Applicants submit that indefiniteness analysis requires whether those skilled in the art would understand what is claimed when read in light of the specification (see, e.g., *Morton International, Inc. v. Cardinal Chemical Co.*, 28 U.S.P.Q.2d 1190 (Fed. Cir. 1993)). The specification provides ample guidance showing the selective inhibition of DNA synthesis with the claimed antibodies and under what conditions such synthesis would be inhibited (see, e.g.,

Example 3 and Figures 4 and 7 of the specification). Example 3 shows the use of the claimed antibodies in neutralization assays using CTGF. The specification states:

> The results of these studies indicated that antibodies directed against the C-terminal domain of CTGF selectively inhibited DNA synthesis, but not collagen synthesis. In contrast, the N-terminal domain of CTGF selectively inhibited collagen synthesis, but not DNA synthesis. This data indicated that different regions of the CTGF molecule may be responsible for signaling different biological activities.

To measure the inhibition of DNA synthesis, Applicants measured the incorporation of 3H-Thymidine. Figures 4 and 7 show that relatively small amounts of 3H-Thymidine are incorporated into DNA when anti-CTGF C-terminal antibodies are administered as compared to incorporation of large amounts of 3H-Thymidine when anti-CTGF N-terminal antibodies or no antibodies are administered. The small amount of 3H-Thymidine uptake indicates that only a small amount of DNA is being synthesized as compared to the control.

Applicants respectfully submit that ample guidance is provided in the specification of inhibition of DNA synthesis by the claimed antibodies such that one of skill in the art would understand the metes and bounds of the claims. Accordingly, withdrawal of the rejection is respectfully requested.

The Office further alleges that claim 22 is indefinite. Specifically, the Office alleges that the claim's recitation that the "antibody comprises murine antibody binding region residues" is indefinite, because individual residues are common to all known living species and one cannot determine the species of origin of a single residue. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 22 to recite "wherein the antibody is a murine antibody". Accordingly, withdrawal of the rejection is respectfully requested.

The Office further alleges that claim 37 is indefinite. Specifically, the Office alleges that claim 37 is indefinite because 1) it derives from a canceled claim; and 2) it is allegedly not clear whether the claimed antibody is a human antibody, or a humanized antibody. Without acquiescing to the reasoning offered by the Office, and in order to expedite prosecution of the instant application, Applicants have amended claim 22 to recite "wherein the antibody is a humanized antibody". Accordingly, withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §102

Applicants respectfully traverse the rejection of claims 15, 19, 21-23 and 37 under 35 U.S.C. §102(b) and (f) as allegedly being anticipated by Grotendorst et al. (U.S. Patent No. 5,408,040, hereinafter, the '040 patent).

To anticipate, a single reference must inherently or expressly teach each and every element of claimed invention. *In re Spada*, 15 USPQ2d 1655 (Fed Cir. 1990); and *Verdegaal Bros. v. Union Oil Co. of California*, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP § 2131. Further, the claimed invention must be distinct from what is apparently inherent in the reference, and the reference must be enabling to place the allegedly disclosed matter in the possession of the public. *In re Fitzgerald et al.*, 619 F.2d 67, 205 USPQ 594 (CCPA 1980); and *Akzo N.V. v. U.S. Int'l Trade Comm'n*, 1 USPQ2d 1241, 1245 (Fed. Cir. 1986).

Specifically, the Office alleges that the '040 patent describes monoclonal or polyclonal antibodies which specifically bind to CTGF and not to PDGF (claims 2-4), and that antigenic fragments may be used to make the antibodies. Additionally, the Office alleges that the '040 patent also discloses at column 7 that "antibodies were made to synthetic peptides containing the carboxyl sequences of the PDGF protein...which antibodies bound to CTGF" (Office Action,

page 4). The Action further states that the "claims may be anticipated by the anit-PDGF antibodies disclosed in the '040 patent that were used to isolate CTGF, the examiner cannot determine such."

Applicants respectfully submit that the '040 patent does not disclose the specific antibodies of the amended claims. The amended claims are directed to an antibody that specifically binds the C-terminal fragment of CTGF, and not PDGF, wherein the antibody inhibits DNA synthesis, and wherein the C-terminal fragment of CTGF is amino acid residues 4 through 74 of SEQ ID NO: 4 (exon 4) or 75 through 172 of SEQ ID NO:4 (exon 5). The '040 patent discloses antibodies generated to purified PDGF or synthetic peptides containing the amino and carboxyl sequences of the mature PDGF A and B chain molecules (see column 7) but not exon 4 and exon 5 of CTGF specifically. The '040 patent discloses antibodies generated to the entire C-terminal region of PDGF, which are unlike the antibodies of the amended claims directed specifically to exon 4 or exon 5 of the CTGF polypeptide. Accordingly, Applicants respectfully submit that the '040 patent fails to teach each and every element of the claimed invention and therefore request withdrawal of the rejection.

Rejections under 35 U.S.C. §103

Applicants respectfully traverse the rejection of claims 15, 19, 21-23 and 37 under 35 U.S.C. §103(a) as allegedly being obvious over Grotendorst et al. (the '040 patent). The recent U.S. Supreme Court decision in the KSR International v. Teleflex Inc. (82 USPQ 2d 1385), modified the standard for establishing a *prima facie* case of obviousness. Under the KSR rule, three basic criteria are considered. First, some suggestion or motivation to modify a reference or to combine the teachings of multiple references still has to be shown. Second, the combination has to suggest a reasonable expectation of success. Third, the prior art reference or combination has to teach or suggest all of the recited claim limitations. Factors such as the general state of the

art and common sense may be considered when determining the feasibility of modifying and/or combining references.

Specifically, the Action alleges that the '040 patent puts into the hands of the public antibodies to the C-terminus of CTGF, via it's teachings of making monoclonal and polyclonal antibodies to CTGF and the teaching of making antibodies to synthetic peptide fragments of PDGF. Applicants respectfully disagree for the following reasons.

Applicants submit that the '040 patent is not *prima facie* obvious over the claimed invention because there is no suggestion or motivation to modify the reference. The '040 patent does not disclose the differing biological activities of the N-terminal and C-terminal regions of the CTGF polypeptide and specifically exon 4 or exon 5. Thus, there is no motivation or suggestion to generate antibodies that specifically bind exon 4 and exon 5. Additionally, the discovery that the claimed antibodies mediate the biological activity of CTGF to inhibit DNA synthesis is unexpected and surprising and not suggested in the '040 patent. Accordingly, the '040 patent did not put into the hands of the public, the antibodies of the claimed invention as the Office suggests.

Applicants respectfully traverse the rejection of claim 20 under 35 U.S.C. §103(a) as allegedly being obvious over Grotendorst et al. (the '040 patent), in view of Hoogenboom et al. (U.S. Patent No. 5,565,332). The '040 patent allegedly teaches the inventions previously stated above. The Action also alleges that Hoogenboom et al. teaches human and humanized antibodies and that it would have been obvious to the person of ordinary skill in the art at the time the invention was made to substitute the anti-CTGF antibodies of the '040 patent into the human or humanized antibodies described in Hoogenboom et al.

Applicants respectfully submit that even if one were to combine the '040 patent with Hoogenboom et al., the resulting combination would not result in the claimed invention since the combined references do not disclose each and every claim limitation (e.g., exon 4 or exon 5 separately). Applicants' invention is directed to an antibody that specifically binds the C-terminal fragment of CTGF, and not PDGF, wherein the antibody inhibits DNA synthesis, and wherein the C-terminal fragment of CTGF is amino acid residues 4 through 74 of SEQ ID NO: 4 (exon 4) or 75 through 172 of SEQ ID NO:4 (exon 5) and the '040 patent alone or combined with Hoogenboom et al. do not provide the claimed antibodies. Accordingly, Applicants submit that a *prima facie* case of obviousness has not been established and withdrawal of the rejection is respectfully requested.

Double patenting rejection

Claims 15, 19, 21-23 and 37 are rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 2-4 of Grotendorst et al. (the '040 patent). Additionally, claim 20 is rejected on the ground of nonstatutory obviousness-type double patenting as allegedly being unpatentable over claims 2-4 of Grotendorst et al. (the '040 patent) in view of Hoogenboom et al. (U.S. Patent No. 5,565,332). Applicants respectfully traverse the rejections as they apply to the pending claims.

As discussed above, the claimed invention is drawn to a C-terminal CTGF antibody directed to amino acid residues 4 through 74 or 75 through 172 of SEQ ID NO:4. For reasons discussed above, the '040 patent alone or in combination with Hoogenboom et al., does not render obvious Applicants' claimed invention which is "patentably distinct" from the cited references. Therefore, there is no basis of nonstatutory obviousness-type double patenting.

Accordingly, withdrawal of the rejection of claims 15, 19, 20-23 and 37 under nonstatutory obviousness-type double patenting is respectfully requested.

Conclusion

In summary, for the reasons set forth herein, Applicants submit that the claims clearly and patentably define the invention and respectfully request that the Examiner withdraw all rejections and pass the application to allowance. If the Examiner would like to discuss any of the issues raised in the Office Action, the Examiner is encouraged to call the undersigned so that a prompt disposition of this application can be achieved.

The Commissioner is hereby authorized to charge $60.00 as payment for the One-Month Extension of Time fee for small entity status to Deposit Account No. 07-1896. Applicants do not believe any other fees are due in connection with the filing of this paper. However, the Commissioner is hereby authorized to charge any other fees associated with the filing submitted herewith, or credit any overpayments to Deposit Account No. 07-1896 referencing the above-identified attorney docket number.

Respectfully submitted,

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